Acute Coronary Syndrome and Crystal Methamphetamine Use: A Case Series

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Abstract

"Ice" is a form of methamphetamine commonly used as a recreational drug in Hawaii and the Philippines, but seldom encountered in the continental United States. It differs in appearance from methamphetamine tablets, but otherwise has exactly the same molecules, only arranged in a crystalline structure. A sizeable body of invitro, animal, and autopsy data suggest a linkage between methamphetamine use and myocardial pathology. In this report, we describe a series of eight patients who developed unstable angina or acute myocardial infarction in association with smoking crystal methamphetamine. The findings, to a large extent, resemble those with cocaine-associated acute coronary syndromes. Given the widespread abuse of methamphetamine among young age groups, the recognition and primary prevention of cardiovascular toxic effects is of mounting socioeconomic importance.

Introduction

Stimulation of central nervous system by methamphetamine leads to a multitude of psychobehavioral manifestations including euphoria, increased energy and self-confidence, and enhanced sexuality. Irritability, insomnia and, when taken in vary large quantities, impaired judgment are its unwanted effects. Acute toxicity may also lead to irrational and violent behavior, delerium, paranoia, hallucinations, homicide or suicide.[1,2] With chronic use, irreversible structural brain damage may occur.[3] Many of the symptoms produced resemble those produced by cocaine use, though it is not clear whether the same mechanisms are involved. Very little is known about methamphetamine's ability to initiate or exacerbate acute coronary syndromes. In this report we describe a series of eight patients who developed unstable angina or acute myocardial infarction in association with smoking of crystal methamphetamine.

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Methods and Results

The study was approved by the local institutional review committee. We retrospectively collected demographic and clinical data on eight crystal methamphetamine users. All had been admitted to a tertiary care center in Honolulu, Hawaii, for treatment of acute coronary syndrome, during the period from April 1997 to July 2000. None of the patients had any history of prior myocardial infarction, valvular heart disease, cardiac surgery, and all denied ever having used cocaine or heroin. The patient characteristics are described in table 1. Their mean age was 37 years (range 23-44). All patients admitted recurrent abuse of "ice", the smokable form of methamphetamine and denied intravenous administration. The specifics of methamphetamine exposure are described in table 2.

Four of the eight patients (50%) had for ST-segment elevation myocardial infarction, while 3 of 8 (38%) and 1 of 8 (12%) were diagnosed with non-ST-segment elevation myocardial infarction and unstable angina respectively. The clinical characteristics of their acute coronary syndromes are described in table 3.

Table 4 describes the investigational findings in this cohort. Of the 6 patients who underwent cardiac catheterization, 5 were shown to have obstructive coronary artery disease with the remaining patient having clean coronary arteries. Two patients refused invasive management. All patients survived the index hospitalization and were discharged home in stable condition.

Discussion

In this case series, we report eight patients who developed acute coronary syndromes in association with the smoking of crystal methamphetamine. The features of this cohort – young age group, predominant representation of native Hawaiian ethnicity and universal use of "ice" as the mode of drug used – represent the general characteristics of a methamphetamine user in Hawaii. Their presentations represented the entire spectrum of acute coronary syndromes, including unstable angina, non- ST elevation myocardial infarction and ST elevation myocardial infarction. Of the 6 patients who underwent coronary angiography, 5 had evidence for significant obstructive epicardial coronary artery disease. In 2 patients, findings suggestive of coronary vasospasm or small vessel disease were present, as demonstrated by a normal coronary angiogram in one patient and a normal nuclear myocardial perfusion study in another patient.

A survey of the English medical literature reveals only 15 similar case reports of myocardial infarction

associated with the use of amphetamine related compounds.[4-18] A summary of previously published case reports is shown in table 5. By contrast, the literature is replete with cases of acute myocardial infarction after cocaine use.[19]

During the past 15 years, the use of methamphetamine has increased dramatically in Hawaii, the Pacific coast and the south/mid west of the United States. The 2000 National Household Survey on Drug Abuse estimated that 8.8 million Americans used methamphetamine in their life time. This figure shows a marked increase from the 1994 estimate of 3.4 million. In comparison, 24.8 million Americans had used cocaine in their life time [20,21]

Methamphetamine is the N-methyl homologue of amphetamine (figure 1). It is a white, odorless, bitter, crystalline powder that is soluble in water and alcohol.[22] It can be smoked, snorted, ingested or injected intravenously. The preferred route of methamphetamine administration varies among geographical regions. A report in 1997 showed that 92% of methamphetamine users in Honolulu preferred the smokable form compared to 32% in San Diego and 11% in San Francisco.[23] The predominant mode of methamphetamine administration in San Diego was sniffing (38%) where as in San Francisco it was intravenous injections (57%).[23]

Methamphetamine is called by many names, including "crank", "speed", "tweak", "go-fast", "go", "glass", "crystal meth", "cris" or "cristy". "Ice" is a common street name in Hawaii for crystal methamphetamine, and is named for its resemblance to chunks of translucent glass. Among the Filipino expatriate community in Hawaii, crystal methamphetamine has been known as "batu", meaning "rock" in Tagalog language.[2]

Amphetamine related compounds exert their physiological effects predominantly by releasing catecholamine neurotransmitters form the adrenal medulla and the nerve terminals. This leads to increased levels of circulating catecholamines and the stimulation of central and peripheral alpha and beta adrenergic receptors.

Table 1. — Patient Characteristics

Patient Number	Age/Gender	Ethnicity	Traditional Cardiac Risk Factors	Significant Past Medical History
1	35/M	Portugese	HTN	none
2	34/F	Caucasian	HTN, Tob, HC	none
3	40/M	Hawaiian	Tob, HC, FH	none
4	44/F	Japanese	HTN	none
5	23/M	Caucasian	none	none
6	43/M	Filipino	HTN, Tob	drug induced psychosis
7	38/F	Hawaiian	Tob	none
8	39/F	Hawaiian	HTN, Tob, HC	none

M=male, F=female, HTN=hypertension, Tob=at least 5 pack year tobacco smoking, HC=hypercholesterolemia (total cholesterol >230mg/dl)

Table 2. — Specifics of Methamphetamine Exposure

Patient Number	Verification	Type	Current Abuse	Frequency	Duration	Last Dose	Alcohol	Other
1	Hx	Ice	Yes	NR	9 yrs	2 hrs	Yes	No
2	Hx	Ice	Yes	NR	NR	NR	No	No
3	Hx	Ice	Yes	1/wk	6 mo	12 hrs	Yes	No
4	Hx,Utox	Ice	Yes	1-2/wk	NR	1 hr	Yes	No
5	Hx	Ice	Yes	NR	NR	NR	No	No
6	Hx,Utox	Ice	Yes	1-2/wk	NR	48 hrs	No	No
7	Hx	Ice	No	NR	NR	1 mo	Yes	No
8	Hx,Utox	Ice	Yes	NR	NR	2 hrs	No	No

Hx=patient history, Utox=urine toxicology, wk=week, yrs=years, mo=months, hrs=hours, NR=not recorded, Last dose= intake time prior to presentation to the hospital, Alcohol=concurrent alcohol use per history, Other= concurrent use of other recreational drugs than methamphetamine per history or urine drug screening

Table 3. — Clinical Characteristics

Patient Number	Presenting Symptims	Symptom Duration	Vital Signs at Presentation			Electrocardiographic Changes at Presentation	Cardiac Injury Markers Maximum Recored		
			T	BP	HR		CK	CKMB	cTnI
1	Chest pain, dyspnea	NR	97.0	159/81	140	Abnormal Q-waves in leads III, aVF; T-wave inversions in lead III	205	8.4	2.2
2	Chest pain, dyspnea	8 hours	98.4	105/78	60	ST-segment elevation in leads aVL, V2-V5	5756	80	150
3	Chest pain	6 hours	98.0	140/90	100	ST-segment depression in lead V4-6	1638	193	130
4	Chest pain, dyspnea	1 hour	97.7	193/98	128	ST-segment depression in leads I, II, aVL; T-wave inversions in leads I, II, aVL, V3-V6	NR	3.2	<0.5
5	Chest pain	2 hours	98.0	130/90	66	ST-segment elevation in leads II, III, aVF, V4-V6	953	141	36
6	Chest pain	24 hours	96.8	140/94	80	ST-segment elevation in leads II, III, aVF; T-wave inversions in leads III, aVF	1727	154	150
7	Chest pain	2 hours	96.7	170/120	77	ST-segment elevation in leads V2-V4	1087	NR	NR
8	Chest pain	2 hours	98.5	202/125	92	T-wave inversions in leads V2-V6	145	10	4.8

NR=not recorded, T=temperature (in °F), BP=blood pressure (in mmHg), HR=heart rate (beats per minute), CK=creatine kinase (normal range 10-70 U/L), CKMB=creatine kinase MB fraction (normal range 0-7 microg/L), cTnI=cardiac troponin I (normal range 0-0.4 microg/L)

Table 4. — Investigational Findings

Patient Number	Cardiac Catheterization	Use of Thrombolytics	Angiographic Findngs	Successful Angioplasty	Echocardiography	Myocardial Perfusion Scanning
1	Yes	No	70% lesion in proximal RCA; distal occlusion of circumflex	No (Attempted)	NWM, LVEF 65%	NP
2	Yes	Yes	50% lesion in proximal LAD; 70% lesion in proximal first diagonal; LVEF 43%; akinesis of distal anterior wall and apex	NP	NP	NP
3	Yes	No	90% lesion in proximal first diagonal	Yes	NWM, LVEF 60%	anterior wall ischemia
4	No	No	No	NP	NP	NP
5	Yes	No	Normal coronary arteries; hypokinesis of apex; LVEF 40-50%	NP	NP	small zone of anterolateral ischemia
6	Yes	No	90% occlusion of proximal RCA; no wall motion abnormality; LVEF 60%	Yes	NP	NP
7	Yes	No	90% occlusion of proximal LAD; hypokinesis of anterior wall	No (Attempted)	LVEF 58%	NP
8	No	No	No	NP	NP	no evidence of ischemia

RCA=right coronary artery, LAD=left anterior descending artery, LVEF=left ventricular ejection fraction, NP=not performed , NWM=normal wall motion

Table 5. — Summary of cases of myocardial infarction associated with amphetamine related compounds, previously published in the English medical literature.

Ref. Number	Age (Yrs)/Gender	Agent, Dose and Route of Administration	Timing of Administration (time prior to admission)	Coronary Arteries per Angiography
4	49/F	metaraminol,IV	minutes	NR
5	22/M	propylhexedrine, PO	several hours	NR
6	14/M	amphetamine, PO	3-4 months	normal
7	58/M	dextroamphetamine, PO	possibly hours	NR
8	22/F	amphetamine, IV	10 hours	normal
9	24/M	amphetamine, 20-50 mg, IV	5 hours	normal
10	33/M	amphetamine, 60 mg, IV	1 hour	normal
11	41/M	crystal methamphetamine, intranasal	1 1/2 hours	Mid RCA thrombus
12	27/M	amphetamine, 1.5 gm, IV	4 hours	normal
13	31/F	crystal methamphetamine, intranasal	NR	normal*
14	37/F	amphetamine, IV	NR	normal
15	42/M	amphetamine, intranasal	20 minutes	NR
16	29/F	amphetamine, PO	NR	prox. LAD
17	35/M	methamphetamine, intranasal	hours	90% prox.
18	31/M	amphetamine, 4 doses, IV	8 hours	NR

*** per autopsy, M=Male, F=Female, NR=Not Recorded, PO=Peroral, IV=Intravenous, RCA= Right Coronary Artery, Prox. LAD= Proximal Left Anterior Descending Artery**

Thus, there is a fundamental similarity between the effects of amphetamines, cocaine and other states characterized by high circulating levels of catecholamine. In addition, amphetamines increase the catecholamine levels in the synaptic cleft by inhibiting the enzyme monoamine oxidase in the nerve terminals.[1,24] Amphetamines may also have a direct stimulating effect on end organs.[25]

The intake of amphetamine related compounds commonly leads to cardiovascular manifestations such as tachycardia, chest pain and hypertension.[3,26-35] At higher doses tachyarrhythmias have been described.[36,37] Several case reports have previously ascribed amphetamines also to a multitude of cardiac and vascular pathology including cardiomyopathy,[8,9,13,38-42] acute pulmonary edema,[13,43,44] necrotizing vasculitis,[45-47] endocarditis,[46,48] pulmonary hypertension,[49] aortic dissection[50,51] cerebral arteritis,[52] ischemic stroke or transient ischemic attacks,[53,54] cerebrovascular hemorrhage[46,48,55-59] and sudden cardiac death.[46,49,60]

Autopsy studies have shown that premature and multivessel coronary artery disease occurs at a much higher rate in methamphetamine users than in age-matched controls.[50] Based upon animal studies, some

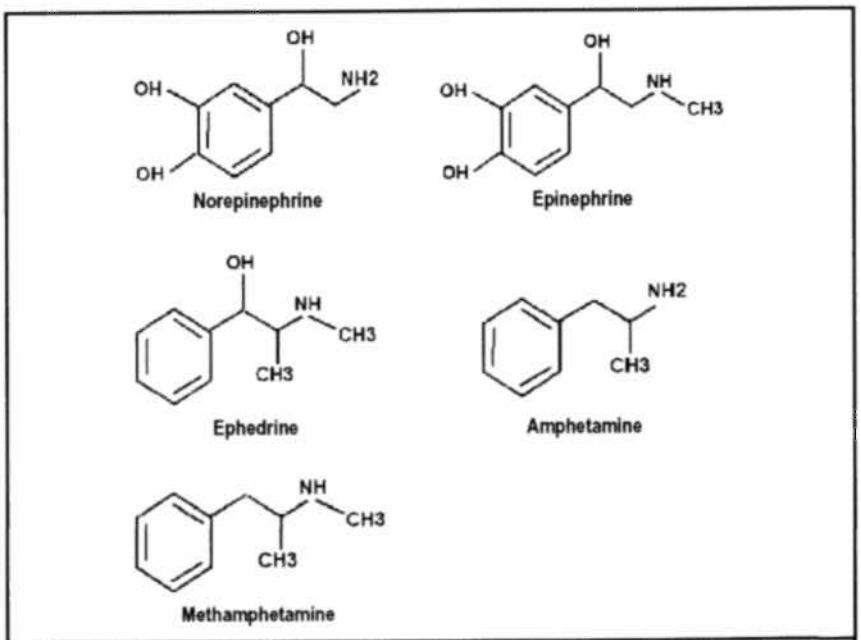

Figure 1. — Chemical Structures of Methamphetamine and Related Compounds

authors have postulated that the increase in circulating catecholamine levels produced by amphetamines could enhance coronary tone and aggregation of platelets, leading to thrombus formation and acute vascular occlusion.[15,30,61] Animal studies have also suggested the possibility of diffuse myocardial inflammation and necrosis induced by high catecholamine levels.[62,67] In the hitherto published cases (including the current case series), of 16 patients who underwent coronary angiography or autopsy 50% (8 of 16) had normal coronary arteries while the other 50% (8 of 16) had evidence of single or multivessel disease. Hence, the occurrence of acute coronary syndrome in the setting of methamphetamine exposure, raises the possibility of rupture of a vulnerable atherosclerotic plaque and/or extensive coronary vasospasm,[13] resembling the acute myocardial ischemia observed in cocaine users.

Despite the observed association between methamphetamine use, development of premature atherosclerosis and induction of acute coronary syndromes, several issues remain unsolved and need to be addressed.

1) Although the rationale for such an association seems intuitive, current data on this subject are limited to individual clinical observations. Hence despite a compelling case, current data do not indisputably establish a causal link between methamphetamine use and acute coronary syndromes. Recent studies have shown that contamination of illicit methamphetamine with chloroephedrine, other organic compounds and heavy metals may have toxic consequences.[68,69] Future case-control studies may minimize potential comorbidities and/or confounders and examine this association more elaborately.

2) Despite apparent resemblance in pathophysiology, methamphetamine related myocardial infarction is far less commonly observed than cocaine related myocardial infarction. While this could be due to lower incidence of methamphetamine use compared to cocaine use in the population, inadequate history taking, incomplete drug screening and underreporting by health care providers may also account for the difference in prevalence of these two conditions. Recent studies on experimental animals have also provided insights into molecular biological disparities between amphetamine and cocaine. Amphetamine, when compared with cocaine, leads to a greater degree of induction of myocardial heat shock proteins. With more heat shock proteins in the cytoplasm, myocytes become more resistant to stressors such as ischemia and injury.[70,71] Consequently, methamphetamine may cause less myocardial damage than cocaine.[58]

3) Recent evidence also suggests that methamphetamine exposure is associated with the development of dilated cardiomyopathy even in the absence of obstructive coronary artery disease.[42] Possible explanations for the development of dilated cardiomyopathy in these patients include small vessel disease, recurrent coronary vasospasm or direct myocardial toxicity due to chronic methamphetamine intake. However, the exact pathophysiologic mechanisms leading to the manifestation of dilated cardiomyopathy with methamphetamine exposure remain to be elucidated.

4) The current treatment strategy of methamphetamine related acute coronary syndrome largely derives from our current understanding of the treatment of this condition in the general population. If coronary vasospasm is considered to be a cause, the use of beta adrenergic blockers may be contraindicated, as it may lead to unopposed alpha adrenergic receptor stimulation and worsening of vasospasm. In this setting, a non-dihydropyridine calcium-channel blocker and aspirin may provide a useful therapeutic combination.[16] Along the lines of recent trials emphasizing the superiority of invasive therapy as opposed to thrombolytic therapy in acute myocardial infarction[72-74], defining the coronary anatomy is likely to be the strategy of choice for reperfusion in patients present with methamphetamine associated acute coronary syndromes. Last, but not least, the active involvement of psychiatric and social services with the aim of prevention, rehabilitation and abstinence from crystal methamphetamine use should be the corner stone in the management of these patients.

Limitations of Study

Like all observational studies, this case series has certain limitations. Only half of the individuals included in this study underwent drug screening, so other drugs may have gone undetected, and it is possible that the clinical course of these individuals could have been modified by their prior use of other recreational drugs. The actual doses taken are not known with certainty, and blood concentrations were not recorded in any of the cases, so the course of the symptoms cannot be related to methamphetamine's pharmacokinetic effects. As in all observational studies, conclusions about causality cannot be drawn with certainty. In addition the patients were not followed up prospectively and data on long-term prognosis are not known.

Conclusion

Several layers of evidence suggest that methamphetamine use is associated with the development of cardiovascular pathology, including accelerated atherosclerosis and premature acute coronary syndromes. Our observations suggest that crystal methamphetamine is associated with acute coronary syndrome in some patients. Given the widespread abuse of methamphetamine among young age groups, the recognition and primary prevention of cardiovascular toxic effects is of mounting socioeconomic importance. Increasing the awareness of the public and of the health care providers about the catastrophic cardiovascular consequences of methamphetamine use is imperative. It is also important to pursue further research in to elucidating pathophysiological mechanisms and developing management strategies.

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References

1. Karch SB. *Karch's Pathology of Drug Abuse*. 3rd ed. Florida: CRC Press; 2002.
2. Wolkoff DA. Methamphetamine abuse: an overview for healthcare professionals. Hawaii Med J 1997;56:34-6, 44.
3. Chiang WK. Amphetamines. In: Goodfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, Howland MA, Hoffman RS, eds. Goodfrank's Toxicologic Emergencies. Stamford: Appleton & Lange; 1998;1091-103.
4. Smith O, Logue B. Arrhythmias and cardiac arrest induced by metaraminol (aramine) bitartrate. JAMA 1960;174:163-66.
5. Marsden P, Sheldon J. Acute poisoning by propylhexedrine. Br Med J 1972;1:730.
6. Schatz IJ, Mizukami H, Gallagher J, Greenslit FS. Myocardial infarction in a 14-year-old boy with normal coronary arteriograms. Studies of blood oxygen release rates. Chest 1973;63:963-9.
7. Orzel JA. Acute myocardial infarction complicated by chronic amphetamine use. Arch Intern Med 1982;142:644.
8. Call TD, Hartneck J, Dickinson WA, Hartman CW, Bartel AG. Acute cardiomyopathy secondary to intravenous amphetamine abuse. Ann Intern Med 1982;97:559-60.
9. O'Neill ME, Arnolda LF, Coles DM, Nikolic G. Acute amphetamine cardiomyopathy in a drug addict. Clin Cardiol 1983;6:189-91.
10. Carson P, Oldroyd K, Phadke K. Myocardial infarction due to amphetamine. Br Med J (Clin Res Ed) 1987;294:1525-6.
11. Furst SR, Fallon SP, Reznik GN, Shah PK. Myocardial infarction after inhalation of methamphetamine. N Engl J Med 1990;323:1147-8.
12. Packe GE, Garton MJ, Jennings K. Acute myocardial infarction caused by intravenous amphetamine abuse. Br Heart J 1990;64:23-4.
13. Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. JAMA 1991;265:1152-4.
14. Ragland AS, Ismail Y, Arsura EL. Myocardial infarction after amphetamine use. Am Heart J 1993;125:247-9.
15. Huang CN, Wu DJ, Chen KS. Acute myocardial infarction caused by transnasal inhalation of amphetamine. Jpn Heart J 1993;34:815-8.
16. Bashour TT. Acute myocardial infarction resulting from amphetamine abuse: a spasm-thrombus interplay? Am Heart J 1994;128:1237-9.
17. Farnsworth TL, Brugger CH, Malters P. Myocardial infarction after intranasal methamphetamine. Am J Health Syst Pharm 1997;54:586-7.
18. Waksman J, Taylor RN, Jr., Bodor GS, Daly FF, Jolliff HA, Dart RC. Acute myocardial infarction associated with amphetamine use. Mayo Clin Proc 2001;76:323-6.
19. Kloner RA, Rezkalla SH. Cocaine and the heart. N Engl J Med 2003;348:487-8.
20. *Office of Applied Studies: Summary of findings from the 2000 National Household Survey on Drug Abuse*. DHHS Publication No. NHSDA Series H-13, (SMA) 01-3549. Rockville, MD: Substance Abuse and Mental Health Services Administration. 2001
21. Methamphetamine [Drug Enforcement Administration Home Page] Available at http://www.usdoj.gov/dea/concern/meth.htm. Accessed 2002/11/18
22. MacKenzie RG, Heischober B. Methamphetamine. Pediatrics in Review 1997;18:305-09.
23. Community Epidemiology Work Group [National Institute on Drug Abuse Home Page] Available at http://www.nida.nih.gov. Accessed 01/21/2003
24. Cho AK. Ice:A new dosage form of an old drug. Science 1990;249.
25. Derlet RW, Horowitz BZ. Cardiotoxic drugs. Emerg Med Clin North Am 1995;13:771-91.
26. Stek AM, Fisher BK, Baker RS, Lang U, Tseng CY, Clark KE. Maternal and fetal cardiovascular responses to methamphetamine in the pregnant sheep. Am J Obstet Gynecol 1993;169:888-97.
27. Derlet RW, Rice P, Horowitz BZ, Lord RV. Amphetamine toxicity: experience with 127 cases. J Emerg Med 1989;7:157-61.
28. Perez-Reyes M, White WR, McDonald SA, Hill JM, Jeffcoat AR, Cook CE. Clinical effects of methamphetamine vapor inhalation. Life Sci 1991;49:953-9.
29. Cook CE, Jeffcoat AR, Hill JM, Pugh DE, Patetta PK, Sadler BM, et al. Pharmacokinetics of methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride. Drug Metab Dispos 1993;21:717-23.
30. Beebe DK, Walley E. Smokable methamphetamine ('ice'): an old drug in a different form. Am Fam Physician 1995;51:449-53.
31. Albertson TE, Derlet RW, Van Hoozen BE. Methamphetamine and the expanding complications of amphetamines. West J Med 1999;170:214-9.
32. Richards JR, Bretz SW, Johnson EB, Turnipseed SD, Brofeldt BT, Derlet RW. Methamphetamine abuse and emergency department utilization. West J Med 1999;170:198-202.
33. Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert HJ, Kovar KA, Lindenblatt H, et al. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. Psychopharmacology (Berl) 1999;142:41-50.
34. Henry JA. Amphetamines. In: Ford MA, Delaney KA, Ling LJ, Erikson T, eds. Clinical Toxicology. Philadelphia: W.B.Saunders Company; 2001;620-26.
35. Varner KJ, Ogden BA, Delcarpio J, Meleg-Smith S. Cardiovascular responses elicited by the "binge" administration of methamphetamine. J Pharmacol Exp Ther 2002;301:152-9.
36. Lucas PB, Gardner DL, Wolkowitz OM, Tucker EE, Cowdry RW. Methylphenidate-induced cardiac arrhythmias. N Engl J Med 1986;315:1485.
37. Morgan JP. Amphetamine and methamphetamine during the 1990s. Pediatr Rev 1992;13:330-3.
38. Smith HJ, Roche AH, Jausch MF, Herdson PB. Cardiomyopathy associated with amphetamine administration. Am Heart J 1976;91:792-7.
39. Croft CH, Firth BG, Hillis LD. Propylhexedrine-Induced Left Ventricular Dysfunction. Ann Intern Med 1982;97:560-61.
40. Ayres PR. Amphetamine cardiomyopathy. Ann Intern Med 1983;97:110.
41. Jacobs LJ. Reversible dilated cardiomyopathy induced by methamphetamine. Clin Cardiol 1989;12:725-7.
42. Wijetunga M, Seto T, Lindsay J, Schatz I. Crystal methamphetamine associated cardiomyopathy: Tip of the iceberg? J Tox Clin Tox 2003;7:1007-1012.
43. Nestor TA, Tamamoto WI, Kam TH, Schultz T. Acute pulmonary oedema caused by crystalline methamphetamine. Lancet 1989;2:1277-8.
44. Maury E, Darondel JM, Buisinne A, Guitton C, Offenstadt G. Acute pulmonary edema following amphetamine ingestion. Intensive Care Med 1999;25:332-33.
45. Citron BP, Halpern M, McCarron M, Lundberg GD, McCormick R, Pincus IJ, et al. Necrotizing angiitis associated with drug abuse. N Engl J Med 1970;283:1003-11.
46. Kalant H, Kalant OJ. Death in amphetamine users: causes and rates. Can Med Assoc J 1975;112:299-304.
47. Bingham C, Beaman M, Nicholls AJ, Anthony PP. Necrotizing renal vasculopathy resulting in chronic renal failure after ingestion of methamphetamine and 3,4-methylenedioxymethamphetamine ('ecstasy'). Nephrol Dial Transplant 1998;13:2654-55.
48. Logan BK, Fligner CL, Haddix T. Cause and manner of death in fatalities involving methamphetamine. J Forensic Sci 1998;43:28-34.
49. Anderson RJ, Garza HR, Garriott JC, Dimaio V. Intravenous prophylhexedrine (Benzedrex) abuse and sudden death. Am J Med 1979;67:15-20.
50. Karch SB, Stephens BG, Ho CH. Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicologic profiles. J Forensic Sci 1999;44:359-68.
51. Swalwell CI, Davis GG. Methamphetamine as a risk factor for acute aortic dissection. J Forensic Sci 1999;44:23-6.
52. Mourand I, Ducrocq X, Lacour JC, Taillandier L, Anxionnat R, Weber M. Acute reversible cerebral arteritis associated with parenteral ephedrine use. Cerebrovasc Dis 1999;9:355-7.
53. Fornazzari L, Carlen PL, Kapur BM. Intravenous abuse of propylhexedrine (Benzedrex) and the risk of brainstem dysfunction in young adults. Can J Neurol Sci 1986;13:337-9.
54. Rothrock JF, Rubenstein R, Lyden PD. Ischemic stroke associated with methamphetamine inhalation. Neurology 1988;38:589-92.
55. Harrington H, Heller A, Dawson D, Caplan L, C. C. Intracerebral hemorrhage and oral amphetamine. Arch Neurol 1983;40:503-7.
56. Davis GG, Swalwell CI. Acute aortic dissections and ruptured berry aneurysms associated with methamphetamine abuse. J Forensic Sci 1994;39:1481-5.
57. Davis GG, Swalwell CI. The incidence of acute cocaine or methamphetamine intoxication in deaths due to ruptured cerebral (berry) aneurysms. J Forensic Sci 1996;41:626-8.
58. Karch S. The problem of methamphetamine toxicity. West J Med 1999;170:232.
59. Moriya F, Hashimoto Y. A case of fatal hemorrhage in the cerebral ventricles following intravenous use of methamphetamine. Forensic Sci Int 2002;129:104-9.

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60. Katsumata S, Sato K, Kashiwade H, Yamanami S, Zhou H, Yonemura I, et al. Sudden death due presumably to internal use of methamphetamine. Forensic Sci Int 1993;62:209-15.
61. Haft JI, Kranz PD, Albert FJ, Fani K. Intravascular platelet aggregation in the heart induced by norepinephrine. Microscopic studies. Circulation 1972;46:698-708.
62. Reichenbach DD, Benditt EP. Catecholamines and cardiomyopathy. Human Pathol 1970;1:125-50.
63. Kaiho M, Ishiyama I. Morphological study of acute myocardial lesions experimentally induced by methamphetamine. Nippon Hoigaku Zasshi 1989;43:460-8.
64. He SY. Methamphetamine-induced toxicity in cultured adult rat cardiomyocytes. Nippon Hoigaku Zasshi 1995;49:175-86.
65. Islam MN, Kuroki H, Hongcheng B, Ogura Y, Kawaguchi N, Onishi S, et al. Cardiac lesions and their reversibility after long term administration of methamphetamine. Forensic Sci Int 1995;75:29-43.
66. He SY, Matoba R, Fujitani N, Sodesaki K, Onishi S. Cardiac muscle lesions associated with chronic administration of methamphetamine in rats. Am J Forensic Med Pathol 1996;17:155-62.
67. He SY, Matoba R, Sodesaki K, Fujitani N, Ito Y. Morphological and morphometric investigation of cardiac lesions after chronic administration of methamphetamine in rats. Nippon Hoigaku Zasshi 1996;50:63-71.
68. Varner KJ, Hein ND, Ogden BA, Arsenault JR, Carter KM, Soine WH. Chloroephedrine: contaminant of methamphetamine synthesis with cardiovascular activity. Drug Alcohol Depend 2001;64:299-307.
69. Burton BT, Hevay metal and contaminants associated with illicit methamphetamine production. In: Miller MA, Kozel MJ, eds. *Methamphetamine abuse: Epidemiologic issues and implications.* Research Monograph 115. Rockville, MD: U.S. Department of Health and Human Services, National Institute on Drug Abuse; 1991:47-59.
70. Lindquist S. The heat-shock response. Annu Rev Biochem 1986;55:1151-91.
71. Maulik N, Engelman RM, Wei Z, Liu X, Rousou JA, Flack JE, et al. Drug-induced heat-shock preconditioning improves postischemic ventricular recovery after cardiopulmonary bypass. Circulation 1995;92:II381-8.
72. Fragmin and fast revascularisation during instability in coronary artery disease investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:708-15.
73. Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet. 2002;360:743-51.
74. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy). — Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879-87.

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7. Miller B. et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndrome: a phase-III intergroup study. Ann Hematol 1992; 65: 162-68.
8. Negrin R. et al. Treatment of the anemia of myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor in combination with erythropoietin. Blood 1993; 82: 737-43. stimulating factor in combination with erythropoietin. Blood 1993; 82: 737-43.
9. Pinto A. 5-aza-2'-deoxycytidine (Decitabine) and 5-azacitidine in the treatment of acute myeloid leukemias and myelodysplastic syndromes: past, present and future trends. Leukemia 1993; 7 (suppl 1):51-60.
10. Silverman L. et al. Effects of treatment with 5-azacitidine on the In vivo and In vitro hematopoiesis in patients with myelodysplastic syndromes. Leukemia 1993; 7 (suppl 1): 21-29.
11. Santini V. Differentiation therapy of myelodysplastic syndromes: fact or fiction? Br J of Hematol 1998; 102: 1124-38.
12. Wijermans P. et al. Continuous infusion of low-dose 5-aza-2'-deoxycytidine in elderly patients with high-risk myelodysplastic syndrome. Leukemia 1997; 11: 1-5.
13. Wijermans P. Low-dose 5-aza-2'-deoxycitidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients J of clin Oncology 2000; 18: 956-962.
14. Witte T. et al. Autologous bone marrow transplantation for patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS. Blood 1997; 90: 3853-57.
15. Baylin SB. et al. Alterations in DNA methylation: a fundamental aspect of neoplasia. Cancer Res 1998; 72: 141-196.
16. Rugo H. et al. Compassionate use of subcutaneous 5-azacytidine (AzaC) in the treatment of myelodysplastic syndrome (MDS). Leuk Res 1999:23 (suppl 1)
16. Shadduck RK. 5-azacytidine therapy for myelodysplasia. Leuk Res 1999 23(Suppl 1): 72(abstract)
17. Silverman LR, et al. A randomized controlled trial of subcutaneous azacitidine(AzaC) in patients with the myelodysplastic syndrome (MDS): a study of the Cancer and Leukemia Group B(CALGB). Proc Am Soc Clin Onc 1998; 17: 14a(abstract)
18. Silverman LR, et al. Azacitidine (AzaC) in myelodysplastic syndromes (MDS). CALGB studies 8421 and 8921. Ann Hemat 1994; 68 (suppl 2): 21a(abstract)

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